deep inside the bilayer. This generates a polar environment near Lys288, but leads to unfavorable hydrophobic-polar interactions at neighboring membrane-facing hydrophobic residues in the cytoplasmic-end segments of TM1 (TM1a) and TM7. Analysis of the K288A mutant MD simulations showed that both membrane deformation and water penetration were eliminated, together with the unfavorable hydrophobic-polar interaction at TM1a and TM7. These results connect the hydrophobic mismatch due to the non-conserved Lys288 residue to a key structural element mediating transport, the TM1a segment that has been shown to move outward during substrate transport. In so doing, the results also provide mechanistic insights into how the K288A mutation, a background mutation used in some recent experimental studies, leads to significantly improved transport properties in LeuT.

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Comparison of Interfacial Tyrosine, Tryptophan and Phenylalanine Residues as Determinants of Orientation and Dynamics of Transmembrane Peptides

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Aromatic amino acids often flank the transmembrane alpha helices of integral membrane proteins. By favoring locations within the membrane-water interface of the lipid bilayer, the aromatic residues Trp, Tyr, and Phe may serve as anchors to help stabilize a transmembrane orientation. In this work, we compare the influence of interfacial Trp, Tyr or Phe residues upon the properties of helical transmembrane peptides. For such comparisons, it is critical to start with no more than one interfacial aromatic residue near each end of a transmembrane helix, for example that of GWALP23 (acetyl-GGALW^{5}(LA)$_{6}$LW^{19}LAGA-[ethanol]amide; see J. Biol. Chem. 285, 31723). To this end, we have employed ^{2}H-labeled alanines and solid-state NMR spectroscopy to investigate the consequences of replacing W5 in GWALP23 with Tyr or Phe residues at the same or proximate locations. We find that GWALP23 peptides having Y5, F5, or W5 exhibit essentially the same average tilt in bilayer membranes of DLPC, DMPC, and DOPC. When double Tyr anchors are present, in Y^{4,5}GWALP23, the NMR observables are more subject to dynamic averaging and at the same time less responsive to the bilayer thickness than when a single Tyr or Phe residue occupies position 4 or 5. Interestingly, Y^{4}GWALP23 and Y^{5}GWALP23 show similar low levels of dynamic averaging and have a difference of about 30°-40° in the preferred helix azimuthal rotation angle in each lipid. Decreased dynamics are observed when ring hydrogen bonding is removed as in the case of F^{4,5}GWALP23. We conclude that, in the absence of other functional groups, interfacial aromatic residues determine the preferred orientations and dynamics of membrane-spanning peptides.

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Cyanylated Cysteine used to Observe the Interaction between the CM15 Antimicrobial Peptide and Neutral Lipid Membranes

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Antimicrobial peptides, the first immune response, are known to provide protection against pathogens; there are three proposed pore formation models by which antimicrobial peptides are believed to disrupt membranes. Previous work used the artificial amino acid cyanylated cysteine to confirm that the synthetic hybrid antimicrobial peptide CM15 porates anionic lipid vesicles by the barrel stave mechanism, which requires a single dominant orientation of the peptide on the lipid surface. Recent molecular dynamics results suggest that CM15 might adopt a number of different structures when binding to neutral lipid bilayers, including those made primarily of phosphatidylcholine (PC) lipids. Infrared spectrometry of CM15 variants provides evidence that the lipid bound conformation of CM15 to neutral bilayers varies significantly from that in contact with anionic bilayers. Additionally, circular dichroism experiments give further insight into the different structures of CM15 in contact with neutral lipid membranes.

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Supported Lipid Bilayers at the Air-Water Interface: A Comprehensive Mechanistic Study of the Cyclic Peptoid Ml 2-6 on Model Bacteria Membrane Systems

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In this investigation, three complimentary experimental techniques including atomic force microscopy (AFM), X-ray reflectivity (XR), and epiflourescence microscopy (EFM) were employed to determine the mechanism of action of the antimicrobial cyclic peptoid ML2-6 on model mammalian and bacteria membrane systems. Mammalian and bacterial membranes were mimicked with Langmuir monolayers and supported bilayers both at solid support and at the air-water interface. We introduce a novel approach in which octadecyltrimethoxysilane (OTMS) supported lipid bilayers are used to mimic mammalian and bacterial membranes, which can be probed with X-ray scattering at the air-water interface. ML2-6 was found to be active on all bacteria membrane models, which was deduced by morphological changes observed from AFM and EFM images following the introduction of the peptoid into the system. In addition, XR revealed changes in film thickness and electron-density profile after the addition of ML2-6, consistent with peptoid insertion into phosphatidyl-glycerol (PG) lipid headgroup in both monolayer and bilayer mimics. Conversely, ML2-6 was found to be inactive on all mammalian membrane models investigated, which was concluded form the lack of morphological changes observed from AFM and EFM images when the peptoid was introduced into the system. Furthermore, XR revealed little change in DPPC/Cholesterol film thickness and electron-density profile after the addition of ML2-6. This suggests that ML2-6 may exhibit potential as an antibacterial agent with low cytoxicity to mammalian host cells.

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Phytochemicals Promiscuously Alter Membrane Protein Function and Bilayer Properties

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Biologically active plant phenols (phytochemicals) are a cornerstone of traditional medicine. Phytochemicals have attracted increasing attention from Western medicine, and thousands of studies on their activity are published each year. Phytochemicals exert a broad range of pharmacological effects including being antioxidant, anti-inflammatory, anticarcinogenic and antimicrobial, yet their mechanism(s) of action are usually ill defined. Some better-studied phytochemicals modulate the function of a multitude of unrelated proteins, with few identified binding sites. Different phenolic compounds often affect the same proteins, many of which are membrane-associated. Additionally, in spite of large variations in chemical structure, plant phenols often have synergistic effects. In this context, it may be relevant that phytochemicals generally are hydrophobic/amphipathic and tend to adsorb to lipid bilayers. Phytochemicals therefore could exert some of their actions indirectly by perturbing membrane properties. To test the hypothesis that plant phenols exert their action on protein function by altering lipid bilayer properties, we chose five heavily studied phytochemicals: capsaicin (chili peppers), curcumin (turmeric), EGCG ((-)-epigallocatechin gallate, green tea), genistein (soybeans), and resveratrol (grapes). We measured their propensity to alter bilayer properties using gramicidin A channels, as probes for changes in bilayer material properties, and explored the phytochemicals' effect on various membrane proteins: potassium channels, membrane-anchored metalloproteases, mechanosensitive channels of large conductance and voltage-gated sodium channels. All the tested compounds alter bilayer properties at concentrations consistent with their reported biological activity; they also altered the function of the membrane proteins tested, albeit at varying concentrations. We show that phytochemicals can alter protein function through a bilayer-mediated manner; therefore, any studies on phytochemicals should keep their promiscuity in mind and before claiming specific interactions evaluate the possibility of an indirect membrane mediated mechanism.

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Lipid Membrane Binding of Computationally-Designed DNA Aptamers Specific for Phosphatidylserine

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Recently we applied an entropy based seed-and-grow strategy to design a set of short DNA aptamers (Chem. Biol. Drug Des. 78:1-13). Each member consisting upto 12 nucleotides binds specifically with phospholipid phosphatidylserine (PS). The PS binding aptamers can be used e.g., to diagnose the PS